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UPS OVERNIGHT

February 22, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Dear Sir:

Enclosed please find our comments on the draft guidance for industry entitled "Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling." We request that these comments be considered before this guidance is finalized.

If you have any questions concerning the attached comments, please contact Dr. Peter Hinderling, Director, Clinical Pharmacology, Berlex Laboratories, Inc. He may reached at (973) 276-2206.

Sincerely,

BERLEX LABORATORIES, INC.

June Bray
Vice President
Drug Regulatory Affairs

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Comments by Berlex Laboratories Inc. to the FDA Guidance for Industry " Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis and Impact on Dosing and Labeling "

p.3: first paragraph : The Guidance recommends studies in patients with impaired hepatic function for drugs " if hepatic metabolism and/or excretion account for a substantial portion of the elimination of a drug or active metabolite ". " Substantial " is defined to mean > 20 % hepatic elimination.

It is suggested that the definition be refined to indicate what the > 20 % refers to: dose or fraction of dose absorbed that is hepatically eliminated when the drug is administered by the intended route?

It would be helpful if the Guidance would explain why the value of 20 % is critical. The criticality of this value should be related to definitions of active metabolites and narrow therapeutic range drugs.

It is a well-known fact that estimates of the percentage of the dose truly hepatically eliminated as parent drug and/or metabolite are difficult to obtain in man. In mass balance studies for an orally administered drug, typically estimates of the dose fraction renally excreted as drug and **major** metabolite(s) can be obtained. The determination of these entities in the feces is more difficult. Accounting for 100 % of the dose administered is rarely achieved in mass balance studies. Estimates of the fraction of the dose absorbed that is metabolized do not necessarily reflect hepatic metabolism. These estimates may include presystemic and systemic, extrahepatic elimination (gastrointestinal, renal and/or pulmonary metabolism). The extrahepatic, non-renal elimination may be important with some drugs and/or active metabolites and hepatically impaired patients may not be the critical target population to study with these drugs. Additional hurdles in determining the fraction of the dose of active metabolite(s) hepatically eliminated may include a) the differentiation between systemically available and unavailable metabolites b) accounting for all entities that represent ≥ 20 % of the dose.

It is hoped that in evaluating mass balance studies with less than 100 % recoveries of the dose administered a worst case scenario is not adopted by the Agency and the unaccounted dose fraction considered to be hepatically eliminated.

It is suggested that the Guidance states that appropriate animal data demonstrating significant extrahepatic, metabolic elimination of a drug or active metabolite are recognized by the FDA as evidence, when evaluating the need for a study in hepatically impaired patients.

The guidance recommends that a study in hepatically impaired patients be considered even for drugs with < 20 % hepatic elimination if "in the event of renal failure, one or more of the hepatic pathways of elimination could become important". It is not clear

what the rationale behind this recommendation is. It appears that it would be more meaningful to do this study in patients with severely impaired renal function than in patients with hepatic impairment in whom renal function is difficult to assess. It is well established that severe renal impairment may be associated with decreased liver function. Also drugs with a narrow therapeutic index should be of primary concern in this context.

In conclusion there is a concern that the well intended classification of drugs as proposed in the present version of the Guidance into "substantially" and "not substantially", hepatically eliminated drugs may not be easy to apply in practice. It is feared that- unless labeling restrictions are an acceptable alternative-studies in the hepatically impaired population will have to be conducted with the overwhelming majority of drugs that are given in multiple doses and for whom patients with liver disease are part of the target population. The absence of attempts to define of what constitutes a narrow therapeutic range drug and an active metabolite adds to the difficulty for users of the present Guidance to decide whether or not a study in hepatically impaired patients ought to be conducted.

p.3, Section IIIA. When studies may not be important: The Guidance states that if the drug is gaseous or volatile and the drug and its active metabolite are primarily eliminated via the lungs a study in hepatically impaired subjects may not be important ". This wording could be interpreted to mean that based on historical data one can exclude that e.g. an inhalation anesthetic is metabolized in the liver and the generated metabolite eliminated via the lung.

p.5: 3.Sample Collection and Analysis: It would be helpful if a short outline of the concept were given that is the basis of the recommendations made in this section. The relevance of differences in plasma protein binding (with highly bound drugs) between populations for computations of exposure, clearance and volume of distribution parameters and their comparison across populations should be more clearly stated. The criticality of the extent of hepatic extraction and route of administration for how the relationship between total and unbound drug concentrations at steady- state is changing should be stated for all relevant combinations.

Also, this subsection of the Guidance refers only to multiple dose studies. It this to mean that multiple dose studies ought to be performed if a change in the fraction unbound is anticipated to impact on the relevant parameters of a drug ?

P, 7: Section A. Parameter Estimation: The Guidance proposes determination of the non-renal clearance of parent drug or active metabolites,Clnr, in hepatically impaired patients (provided plasma and urine concentrations are collected). However, it should be realized that unbiased estimates of the oral nonrenal clearance can only be obtained if oral and intravenous data are available and the biovailability,f, is known: Clnr/f=Cl/f - Clr/f.

p.8, First bullet: The Guidance states " If the effect of hepatic impairment on the PK of the drug is obvious (e.g., twofold or greater increase) necessary dosage adjustments should be reflected in the labeling." It is recommended that the Guidance define the target parameter (presumably AUC, or AUC u) in the bracketed term and modify the wording following the brackets as follows " dosage adjustments, if necessary, should be reflected in the labeling".

It is suggested that the Guidance should alert to the possibility that the dose in hepatically impaired patients may have to be increased (or the dose interval shortened for drugs whose activity is due to a predominantly hepatically eliminated metabolite

pp. 8/9/10 : Section VI. Labeling: it should be clarified that the statements made are based on information obtained in a study using the reduced study design

pp. 11/12 : in a previous meeting on individual bioequivalence and narrow therapeutic index drugs it was recommended to use the term therapeutic range instead of therapeutic index. It is suggested that the Agency use a consistent nomenclature.

PHH 2/13/2000

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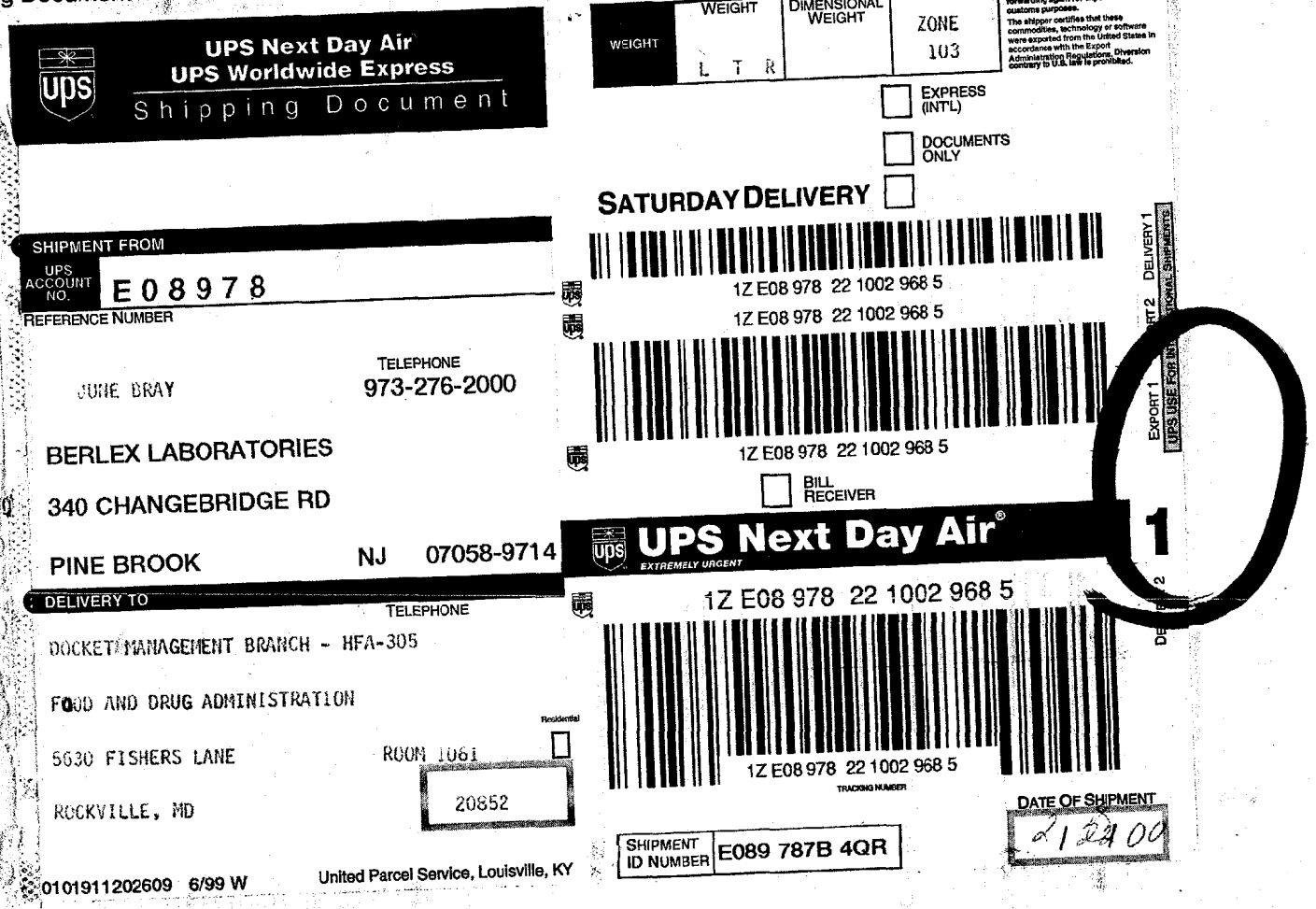

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